In This Issue .................................................. 469

Meet the First Authors ........................................ 470

Editorials
New Initiatives to Improve the Rigor and Reproducibility of Articles
Published in Circulation Research
Roberto Bolli .................................................... 472
Allele-Specific Gene Silencing: Another Step in the Inexorable Advance of Gene Therapy for Cardiac Arrhythmia Management
Stanley Nattel ................................................. 480
When High Throughput Meets Mechanistic Studies: A State-of-the-Art Approach in Brugada Syndrome
Bettina Heidecker ............................................ 483
Besides Imprinting: Meg3 Regulates Cardiac Remodeling in Cardiac Hypertrophy
Shizuka Uchida ............................................... 486

Trainee and Young Investigator Corner
Training for Success
Robert N. Correll ............................................. 488

Promising Young Investigators
Michael Potente: No Time to Waste
Ruth Williams ................................................ 490

News & Views
Cardiovascular Research in Germany
Gerd Heusch, Thomas Eschenhagen, Stefanie Dimmeler ......................... 492

Circulation Research (ISSN 0009-7330 print / 1524-4571 online) is published semimonthly for 24 total issues a year by Wolters Kluwer Health, Inc., at 14700 Citicorp Drive, Bldg 3, Hagerstown, MD 21742. Business offices are located at Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103. Production offices are located at 351 West Camden Street, Baltimore, MD 21201-2436. Individuals may subscribe for their personal use at the following rates for print subscriptions: $225 for AHA/ASA Domestic and International Members (excluding General Membership level), or $790 for domestic non-members and $937 for international non-members. AHA membership information can be found online at professional.heart.org. Periodicals postage paid at Hagerstown, MD, and additional mailing offices. POSTMASTER: Send address changes to Circulation Research, American Heart Association, Wolters Kluwer Health, Inc., PO Box 1610, Hagerstown, MD 21740.
**Viewpoints**

Large Animal Model Efficacy Testing Is Needed Prior to Launch of a Stem Cell Clinical Trial: An Evidence-Lacking Conclusion Based on Conjecture
Stephen E. Epstein, Dror Lugr, Michael J. Lipinski ............................................. 496

Application of PCSK9 Inhibitors in Practice Challenges and Opportunities
Tina M. Kaufman, P. Barton Duell, Jonathan Q. Purnell, Cezary Wójcik, Sergio Fazio, Michael D. Shapiro ............................................. 499

**Molecular Medicine**

Genetic Deletion of NADPH Oxidase 1 Rescues Microvascular Function in Mice With Metabolic Disease

ARHGAP18 Protects Against Thoracic Aortic Aneurysm Formation by Mitigating the Synthetic and Proinflammatory Smooth Muscle Cell Phenotype
Renjing Liu, Lisa Lo, Angelina J. Lay, Yang Zhao, Ka Ka Ting, Elizabeth N. Robertson, Andrew G. Sherrah, Sorour Jarrah, Haibo Li, Zhaoxiong Zhou, Brett D. Hambly, David R. Richmond, Richmond W. Jeremy, Paul G. Bannon, Mathew A. Vadas, Jennifer R. Gamble ............................................. 512

★★ Allele-Specific Silencing of Mutant mRNA Rescues Ultrastructural and Arrhythmic Phenotype in Mice Carriers of the R4496C Mutation in the Rymodine Receptor Gene (RYR2)
Rossana Bongianino, Marco Denegri, Andrea Mazzanti, Francesco Lodola, Alessandra Vollero, Simona Boncompagni, Silvia Fasciano, Giulia Rizzo, Damiano Mangione, Serena Barbaro, Alessia Di Fonso, Carlo Napolitano, Alberto Auricchio, Feliciano Protasi, Silvia G. Priori ............................................. 525

★★ The Brugada Syndrome Susceptibility Gene HEY2 Modulates Cardiac Transmural Ion Channel Patterning and Electrical Heterogeneity

**Cellular Biology**

★★ Transient Notch Activation Induces Long-Term Gene Expression Changes Leading to Sick Sinus Syndrome in Mice
Yun Qiao, Catherine Lipovsky, Stephanie Hicks, Somya Bhatnagar, Gang Li, Aditi Khandekar, Robert Guyz, Kel Vin Woo, Colin G. Nichols, Igor R. Efimov, Stacey Rentschler ............................................. 549

Sirt3 Impairment and SOD2 Hyperacetylation in Vascular Oxidative Stress and Hypertension
Integrative Physiology

**Inhibition of the Cardiac Fibroblast-Enriched IncRNA Meg3 Prevents Cardiac Fibrosis and Diastolic Dysfunction**

Maria-Teresa Piccoli, Shashi Kumar Gupta, Janika Viereck, Ariana Foinquinos, Sabine Samolovac, Freya Luise Kramer, Ankita Garg, Janet Remke, Karina Zimmer, Sandor Batkai, Thomas Thum

575

Letters to the Editor

Letter by El-Battrawy et al Regarding Article, “The Brugada Syndrome Susceptibility Gene HEY2 Modulates Cardiac Transmural Ion Channel Patterning and Electrical Heterogeneity”

Ibrahim El-Battrawy, Siegfried Lang, Martin Borggrefe, Xia-Bo Zhou, Ibrahim Akin

Response by Veerman et al to Letter Regarding Article, “The Brugada Syndrome Susceptibility Gene HEY2 Modulates Cardiac Transmural Ion Channel Patterning and Electrical Heterogeneity”

Christiaan C. Veerman, Ronald Wilders, Arthur A. Wilde, Ruben Coronel, Carol Ann Remme, Arie O. Verkerk, Connie R. Bezzina

575

In June 2017, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 12.45 days.

On the Cover: Volcano plot of HEY2 coexpression analysis in human left ventricular tissue. Genes that are coexpressed with HEY2 in human heart were identified by correlating the abundance of transcripts genome-wide with the abundance of the HEY2 transcript (x-axis, regression coefficient; y-axis, negative log of the P value). The transcript of the KCNIP2 gene, which encodes potassium channel interacting protein 2, was strongly positively correlated with that of HEY2. See related article, page 537.
Circ Res. 2017;121:e21-583

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/121/5

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/